solid support, and wherein said detector layer is comprised of a monolayer of physiologically viable cells; and

(b) detecting a response of the detector layer to the test compound, wherein a response is indicative that a test compound is a bioactive compound.

REMARKS

1. Status of the claims

Claims 18-38 were pending in this application. Claims 18-38 have been canceled and new claims 39-59 have been substituted in their place. These claims were written as new claims because it is believed that this is a more clear presentation of the claimed invention. In particular:

New claims 39 and 58 more clearly define the invention and correspond to original claims 1 and 14. The definition of the array (see page 8, lines 9-11) has been included to clarify that the compounds are positioned on a solid support in such a way that the position in the area of the detector will be correlated with the identify of the compound in the array (see page 31, lines 17-20 of the Specification) and thus, no decoding is necessary when the screening result is obtained. Another clarification is that the array of test compounds are brought

into close application with the detector layer (see page 17, line 3 of the last paragraph of the Specification). Such close application cannot be obtained if the compounds or the cells are in traditional 96 well plates, but is only possible if the compounds or the cells are held on a sheet or similar support. Finally, the new independent claims 39 and 58 recite the use of a response, namely to indicate that the test compound is a bioactive compound.

New claims 40 and 41 correspond to claim 18 and 27. New claim 41 corresponds to claim 27. New claim 42 corresponds to claim 19. New claim 43 corresponds to claim 20. New claims 44 and 56 correspond to claim 26. New claim 45 corresponds to claim 21. New claim 46 corresponds to claim 24. New claim 47 corresponds to claim 25. New claim 48 corresponds to claim 28. New claims 49 corresponds to claim 29 and new claims 50 and 57 correspond to claims 30 and 31. New claim 51 corresponds to claim 32. New claim 52 corresponds to claim 33. New claim 53 corresponds to claim 34. New claim 54 corresponds to claim 35. New claim 55 corresponds to claim 36. New claim 58 represents a combination of claims 18-20. No new matter has been added.

2. Rejections Under 35 USC § 112, second paragraph

The Examiner has rejected claims 18-38 under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. These claims have been cancelled and new claims 39-59 have been added. Applicant has made the appropriate claim amendments in these new claims to overcome the antecedent basis problems and to more clearly define the features and/or the relationship of the features in the claims as suggested by the Examiner. Reconsideration and removal of the rejection is respectfully requested.

A brief description of the new dependent claims and their relationship to the previous claims is presented below.

Claims 40 and 41, based on previous claims 18 and 27, specify the two preferred types of solid support on which the array of test compounds is disposed.

Claims 42 - 48 are based on previous claims 19, 20, 26, 21, 24, 25, and 28, respectively.

Claim 49, based on previous claim 29, relates to the specific embodiment wherein the test compounds are disposed on a porous membrane with specific properties. This allows for diffusion from the porous membrane into a liquid layer overlaying the detector layer. For example, cells in a detector layer will have a liquid layer on top of them. This (usually

very thin) layer of liquid will promote the diffusion of the test compounds through the porous membrane. Because there is only a thin liquid layer, typically in the range 100 to 500µm, between the test array and the porous membrane above, there is rapid contact of compounds with cellular protrusions, and insignificant intermixing of adjacent test compounds. Dissolved compounds then move through the pores of the supporting membrane and into the liquid layer overlaying the cells in the detector layer, and contact the cells from the upper surface.

Claim 50, based on previous claims 30 and 31, relates to the diffusion through a porous membrane to the liquid layer surrounding the detector layer. Thus, the method of the invention allows each test compound disposed on a solid support to come into contact with a limited fluid volume, which fluid volume is in immediate contact with the detector layer.

Claim 51 (previous claim 32) and claim 52 (previous claim 33) relate to specific embodiment of the way of contacting the test compounds with the detector layer. Both claims secure that the contact is being made while an optical detector is capable of measuring the response (within the field of view of an optical detector). This is highly important when measuring transient responses (as illustrated in example 7, Figure 7 of the Specification) or time series (as illustrated in examples 8 and 9, Figures 9, 11 and 13 of the Specification). Signaling

responses, for instance changes in the level of free calcium in cellular cytoplasm, may first be seen within seconds or minutes following delivery of test compounds to the detector layer. The way in which these changes develop within cells (time-response profile) is an important diagnostic feature of the signaling processes giving rise to them.

Claims 53-55 are based on previous claims 34-36.

3. Immediately Allowable Claims

It is noted that claim 20 was not rejected for any reasons under § 112, and was only rejected for prior art reasons over Negulescu et al. But Negulescu et al is not prior art to the present application (see below). Therefore, claim 20 (now claim 59) should be immediately indicated as being allowable.

4. Rejections Under 35 USC §102(b)

Applicant has cancelled claims 18-38 and have substituted new claims 39-55. Applicant submits that the rejections will not apply should the Examiner choose to apply them to the newly presented claims 39-57.

The Examiner has rejected claims 18-19, 21, 23-35 and 24-25 under 35 USC §102(b) as being anticipated by Sittampalam et al. (Current Opinion in Chemical Biology, 1997). The Examiner argues

that this reference describes cell-based assays based on 96-well microtiter plates. Applicant respectfully submit that the compounds stored in the 96-well microtiter plate will never get in close apposition to the cells in the detector layer. Sittampalam specifically states on page 385, at the end of column 1 that "special techniques, instrumentation and reagents compatible with cell-based assays have to be developed". The technique described in the present application is an example of such techniques enabling High Throughput Screening of compounds in cell-based assays. As Sittalpalam does not describe each and every feature of the claimed invention (i.e. does not describe bringing the compounds in close apposition with the detector layer), Applicant submits that Sittalpalam fails to anticipate the claimed invention. Reconsideration and removal of this rejection is requested.

5. Rejections Under 35 USC §102(e)

Applicant has cancelled claims 18-38 and have substituted new claims 39-55. Applicant submits that the rejections will not apply should the Examiner choose to apply them to the newly presented claims 39-57.

5.1 Rejection over Isacoff et al.

The Examiner has also rejected claims 18-19, 21 and 34-35 under 35 USC §102(e) as being anticipated by Isacoff et al. (US 5,756,351). Isacoff et al. is cited for disclosing a method for monitoring the physiological status of a cell and disclosing a method for screening test compounds for bioactivity. The Examiner argues that Isacoff discloses contacting an array of test compounds with a detector layer comprising physiologically viable cells which produces a detectable response indicative of bioactivity. The Applicant cannot find any such language in Isacoff. Isacoff teaches only a modified cell, which comprises an artificial molecular optical sensor. The description of the Isacoff technology in drug screening is found at column 4, lines 20-32. Here, the Isacoff cells are *exposed* to specific chemical signals. This in no way teaches the present invention as described in the claims, wherein the detector layer (the cells) are brought into close apposition with the test compounds supported by a sheet. We respectfully request that the anticipation rejection over Isacoff be withdrawn.

5.2 Rejection over Negules et al.

Claims 18-22, 26, 32-33, 34-35 and 38 have also been rejected under 35 USC §102(e) as being anticipated by Negulescu et al. The 35 USC §102(e) date of this reference is July 21, 1998. In

Applicant's previous response, Applicant amended the Specification to recite the claimed priority to US Provisional Application No. 60/070,792 filed on January 8, 1998 under 35 USC §119(e) more than six months prior to Negulescu et al's filling date. Applicant, therefore, submits that the Negulescu reference is not a proper reference under 35 USC §102(e) and thus, the rejection should be removed.

5.3 Rejection over Chelsky

Claims 18, 21-23, 27-33 and 36-37 have been rejected under 35 USC §102(e) as being anticipated by Chelsky (US 5,856,083). The Examiner states that Chelsky disclose an assay wherein the test compounds are held on porous or non-porous solid support (column 3, lines 30-67, column 5, lines 15-52 and column 6, lines 62-67). Applicant will, respectfully, use this opportunity to rule out a slight misunderstanding. Chelsky does not dispose the compounds in a pattern whereby a compound position can be identified by a simple 2-dimensional coordinate (as the definition of *array* in the present application includes). Chelsky teaches (e.g. column 7 lines 11-43) that when preparing the matrix the solid supports can be in a random arrangement or in an ordered arrangement. Both of these arrangements are formed by letting a suspension of beads dry on the bottom of a petri

plate (random) or on a rigid template with holes sized to allow only a single bead to settle (ordered). Common to both arrangements is the step required after detection of activity: decoding (column 13, line 45). The present invention includes an *array* of test compounds which, by the definition (page 8 lines 9-11 of the present application, now included in step (a) of claim 39) means disposing the compounds in a pattern whereby a compound can be identified by a simple 2-dimensional coordinate. Thus, as Chelsky does not teach such an *array* but merely an *arrangement*, Applicant submits that the present claims are novel over Chelsky. Reconsideration and removal of the rejection is respectfully requested.

6. Rejections Under 35 USC §103(a)

Claim 38 has been rejected under 35 USC §103(a) as being unpatentable over Sittampalam et al. or Chelsky et al. Claim 38 has been cancelled. Accordingly, the Examiner's rejection has been rendered moot.

Applicant believes that the foregoing comments demonstrate the present invention's novelty over the cited prior art references. Accordingly, reconsideration and removal of the rejections is requested. Favorable consideration and entry of the amendment is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at (714) 708-8555, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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By _____

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner of Patents and Trademarks, Washington D.C. 20231 on: 12-26-2001
(Date of deposit)
BIRCH, STEWART, KOLASCH & BIRCH, LLP
(Signature)
December 26, 2001
(Date of Signature)

MARKED-UP VERSION OF THE CLAIMS

IN THE CLAIMS:

39. (New) A method for screening test compounds for bioactivity, comprising:

(a) obtaining an array of test compounds, wherein each test compound is disposed on a solid support in [at] a pattern whereby the [compound] position of each of said test compounds can be identified by a [simple] 2-dimensional coordinate;

(b) bringing the array of test compounds in close apposition with a detector layer; and

(c) detecting a response of the detector layer to the test compounds,

wherein a response is indicative that [the] a test compound is a bioactive compound.

40. (New) The method of claim 39, wherein the solid support is a porous membrane.

41. (New) The method of claim 39, wherein the solid support is a non-porous substrate.

42. (New) The method of claims 39, 40 or 41, wherein the detector layer is comprised of physiologically viable cells.

43. (New) The method of claim 42, wherein the physiologically viable cells form a monolayer.

44. (New) The method of claim 42[or 43], wherein the physiologically viable cells are supported by an optically clear substrate.

45. (New) The method of claims 39, 40 or 41, wherein the response is recorded by a sequence of images.

46. (New) The method of claims 39, 40 or 41, wherein the detector layer is a pH sensing surface.

47. (New) The method of claims 39, 40 or 41, wherein the detector layer is a temperature sensing surface.

48. (New) The method of claim 40, wherein the porous membrane is constructed of a non-absorbent material with pores of regular and defined diameter which traverse the membrane directly from the upper to the lower side.

49. (New) The method of claim 40, wherein the test compounds are allowed to diffuse from the porous membrane into a liquid layer overlaying the detector layer.

50. (New) The method of claim 41 [and 42], wherein the solid support is a non-porous substrate and wherein the cells are grown on a porous membrane, whereby the test compounds are allowed to diffuse though the porous membrane to the cells layer.

51. (New) The method of claims 39, 40 or 41, wherein the detector layer is held stationary in the field of view of an optical detector and the array of test compounds is moved into contact with said detector layer during the course of measurement.

52. (New) The method of claims 39, 40 or 41, wherein the array of test compounds is held stationary in the field of view of an optical detector and the detector layer is moved into contact with said sample surface during the course of measurement.

53. (New) The method of claim 42, wherein the detected response is a change in a luminescence property of the physiologically viable cells in the detector layer.

54. (New) The method of claim 42, wherein the detected response is a change in a fluorescence property of the physiologically viable cells in the detector layer.

55. (New) The method of claim 40, wherein the array of test compounds is generated on the solid support by combinatorial chemistry.

56. (New) The method of claim 43, wherein the physiologically viable cells are supported by an optically clear substrate.

57. (New) The method of claim 42, wherein the solid support is a non-porous substrate and wherein the cells are grown on a porous membrane, whereby the test compounds are allowed to diffuse through the porous membrane to the cells layer.

58. (New) A method for screening test compounds for bioactivity, comprising:
(a) bringing an array of test compounds in close apposition with a detector layer, said array of test compounds being comprised of a plurality of test compounds, each of said test compounds being disposed on a solid support in a pattern whereby the position of each of said test compounds can be identified by a 2-dimensional coordinate; and
(b) detecting a response of the detector layer to the test compound,wherein a response is indicative that a test compound is a bioactive compound.

59. (New) A method for screening test compounds for bioactivity, comprising
(a) contacting an array of test compounds with a detector layer whereby each test compound comes into contact with a localized liquid which is in contact with the detector layer, wherein said

array of test compounds is comprised of a plurality of test compounds, each of said test compounds being disposed on a solid support, and wherein said detector layer is comprised of a monolayer of physiologically viable cells; and

(b) detecting a response of the detector layer to the test compound, wherein a response is indicative that a test compound is a bioactive compound.